Studies in infants and toddlers should only be initiated when data from older children and adolescents have been found acceptable.

Immunological assessment and criteria

Clinical studies should provide a detailed characterisation of immunological responses to the strain in the candidate influenza vaccine, which should be the strain intended for the final product. Data generated during clinical studies conducted with vaccines manufactured similarly but containing other influenza viruses, including other strains with a potential to cause a pandemic or seasonal influenza strains, may be considered to be supportive.

The comprehensive results from the HI, SRH and microneutralisation assays will form the basis for the assessment of immunogenicity. The choice of methodology and the standardisation of the assays should be addressed by the applicant. Applicants should predefine in the protocol which immunogical parameter(s) will be used in the primary analysis of immunogenicity.

The seroprotection criterion of at least 1:40 for the HI titre that is applied to the assessment of immunogenicity of seasonal influenza vaccines is based upon the assumption of a correlation with a reduction in influenza-like illness when most of the vaccinated population has some degree of pre-existing immunity against the vaccine strains. This criterion may not be valid for vaccines prepared from an influenza virus with the potential to cause a pandemic and to which the population would be immunologically naive. Alternative cut-off points should be discussed and possibly justified.

As generally stipulated for vaccines used for primary immunisation of a previously immunologically naïve population, influenza vaccines used for pandemic preparedness should induce high seroprotection rates, preferably after one or at most two doses. All three criteria (seroprotection rate, GMT increase and response rate) as defined in guideline CPMP/BWP/214/96 should be fulfilled.

A demonstration that the candidate vaccine elicits neutralising antibodies directed against the vaccine strain is very important. The neutralising antibody titre that correlates with seroprotection is, at present, unknown. Neutralising antibody should be measured in at least a subset of vaccinated individuals, preferably at one or a few selected reference centres with the appropriate expertise. The proportions achieving at least a fourfold increase in the antibody titre and the GMTs should be reported along with a reverse cumulative distribution curve.

Although additional immunological assessments, such as explorations of cell-mediated immunity and neuraminidase inhibition, are of unknown relevance to protection, these should be explored in a subset of vaccinees to provide more insight into the overall effects of vaccination.

Antibody kinetics after the first and second dose should be described. Immune responses should also be determined at intervals after completion of the primary series in at least a statistically valid subset of the vaccinated population to investigate the need for revaccination. At the time of initial authorisation, these data may be limited (e.g. to 6-12 months for only a subset of the vaccinated population). It will be expected that applicants will have plans in place and commit to follow antibody levels over time (post approval commitment).

Dose and schedule

In order to support the dose and regimen that are proposed in the SPC, studies should evaluate immune responses after single and multiple doses. Anti-HA antibodies should be assessed by means of HI and/or SRH assays. Virus neutralisation should also be assessed after single and multiple doses in at least a subset of vaccinees (see above under immunological assessment and criteria).

The optimal dose and schedule may depend upon:

- Vaccine specific factors, such as type and amount of antigens, content and type of adjuvant;
- Population specific factors such as age, immunological naivety to the strain.

If the data indicate that more than one dose of vaccine is needed to achieve potentially adequate and/or optimal immune responses, consideration should be given to evaluating the minimum dose interval that might be employed.

- Initial dose finding studies

In general, for each specified population group naïve individuals (i.e. HI titre < 1:10) should be studied for each dose and/or proposed schedule that is investigated to identify formulations (e.g. dose of antigen and amount of adjuvant, if needed) and schedules that elicit potentially adequate serological responses. The number of subjects studied per dose group should be statistically justified, but be at least 50.

- Dose confirmatory studies

Once the applicant considers that an appropriate formulation and schedule has been identified for healthy adults aged from approximately 18-60 years, the safety and immunogenicity of the final choice should be evaluated in larger numbers in a similar population. The total database for safety in this first population to be studied should be as shown in table 1 and discussed below. A substantial proportion (to be justified by the applicant) of the additional subjects vaccinated should also be studied for immunogenicity. If some age groups (e.g. persons of a particular decade between 18-60 years) were underrepresented in the initial dose finding study, particular efforts should be made to obtain further data in the dose confirmatory study.

Extension of the population in which the vaccine may be indicated for use (e.g. by age group and/or risk factors) may be based on studies completed before or after initial authorisation.

- Induction of immunity to other influenza strains

As explained above, the primary characterisation of the immune response to a candidate influenza vaccine should focus on assessing the immune responses to the vaccine strain. These data would form the basis for the assessment of immunogenicity before initial authorisation.

However, either before and/or after initial authorisation (see also below) the applicant is expected to investigate or have plans to investigate:

- Cross-reactivity i.e. ability of antibody elicited by the vaccine to react with other viruses in circulation (e.g. cross-reaction of antibody elicited by an H5N1 vaccine to emerging drift variants of H5N1 avian influenza viruses). This should be assessed by means of neutralising antibody tests using different strains in the assay.

- Cross-protection. Information on cross-reactivity as described above may be included in section 5.1 of the SPC. However, no claims for cross-protection can be made unless the cross-reactivity data are supplemented by evidence that vaccinated animals are protected against infection following challenge with other strains.

In addition, applicants are encouraged to investigate the potential for cross-priming i.e. examination of the immune responses of individuals primed with the candidate vaccine to a vaccine containing another strain of virus (see also section 4.3 - Dose and schedule and section 4.4).

Safety

The size of the safety database for each influenza vaccine prepared from a virus with a pandemic potential will be different, depending on the population studied, as defined in table 1.

Table 1:

Size of the safety database required to detect ADRs occurring at a frequency as stated below*:	
Adults from 18 to 60 years	≤ one in one thousand persons vaccinated (i.e. rare ADRs) (e.g. a database of approximately 3000 subject might be sufficient)
Specified age groups (e.g. infants, children, adolescents, adults over 60 years of age)	≤ one in one hundred (i.e. uncommon ADRs) (e.g. a database of approximately 300 subjects from each specified age group might be sufficient)
Specified risk groups (e.g. immune compromised individuals, chronically ill patients)	≤ one in one hundred (i.e. uncommon ADRs) (e.g. a database of approximately 300 subjects from each specified risk group might be sufficient)

* Applicants are encouraged to discuss the proposed size of the safety database with competent regulatory authorities during the clinical development programme.

Follow-up for the evaluation of safety should be at least 6 months after the last dose of vaccine. For reactogenicity evaluation, at least all the parameters defined in guideline CPMP/BWP/2490/00 should be studied. These data should be submitted before initial marketing authorisation.

If any new issues regarding safety arise during the clinical development programme, these need to be adequately addressed before authorisation and followed up specifically as part of the risk management plan.

Post-approval commitments and Risk management plan

As mentioned above, at the time of initial authorisations plans should at least be in place to assess antibody persistence, cross-reactivity and cross-protection to new circulating strains. There should also be definite plans for assessment of responses to booster doses in cohorts of vaccinees from each age and risk group for which an indication has been granted.

Whenever the opportunity arises, such as during any government-directed use of vaccine within cohorts in individual countries, further information should be collected from observational studies to expand the safety and the immunogenicity database. If there is exposure of vaccinees to circulating influenza strains with a potential to cause a pandemic (e.g. persons dealing with avian influenza outbreaks in flocks or close contacts of documented cases of human infection due to such viruses) information on breakthrough cases should be collected. It is especially recommended to collect additional data in populations which have been studied to a lesser extent in the pre-authorisation clinical trials.

In the event of a declared pandemic, monitoring the effectiveness of prior administration of any vaccines containing strains expected to provide some protection (based on cross-reactivity and/or cross protection studies) would be important. Such data would be informative for planning future pre-pandemic vaccination strategies and, if data become available early enough, evidence of protection from prior vaccination could mean that any available pandemic vaccine (i.e. vaccine prepared from the exact influenza strain causing the pandemic) might be directed primarily to previously unvaccinated cohorts.

If the strategy in any one country has been to prime with pre-pandemic vaccine(s) and to administer a dose of pandemic vaccine as soon as it becomes available, then it is recommended that immune responses to the pandemic vaccine should be assessed and compared between any previously vaccinated and unvaccinated cohorts. It may also be possible to monitor the effectiveness of such a strategy provided that the pandemic vaccine can be given early enough to potentially impact on infection rates, complication rates and/or death rates.

In both the instances described, and depending in part on the number of different pre-pandemic vaccines that may have been distributed in a population, it may or may not be possible to assess vaccine-specific protection as well as the overall effectiveness and safety of the chosen strategy. It is acknowledged that monitoring effectiveness and safety under both scenarios will be fraught with difficulties and will need careful pre-planning, most likely in close conjunction with public health authorities. Any plans in this regard should be provided in the Risk Management Plan (RMP) or be included in updates of the RMP.

4.4. Post authorisation issues for influenza vaccines prepared from viruses with pandemic potential

It is possible that MAHs might wish to propose replacement of the strain in an approved vaccine. For example, this might occur if sequential studies show low or negligible cross-reactivity and cross-protection to drift variants and/or if expert opinion suggests that the HA subtype of influenza virus most likely to trigger a pandemic has changed. Two scenarios could occur and have different regulatory implications as follows:

a. Replacement of the strain in the approved vaccine with a different strain of the same subtype (e.g. supplanting the original H5N1 with another H5N1 strain). In this case the MAH would have to submit all manufacturing and quality data related to the new strain. A clinical study should be conducted to demonstrate that immune responses to the new vaccine strain are adequate (see section 4.3: Immunological assessment and criteria). If feasible it is recommended that the vaccine prepared from the replacement strain should also be administered to a cohort that previously received the original strain vaccine in order to assess cross-priming. Applicants are advised to obtain advice from EU competent authorities regarding the extent and type of clinical data that would be required.

b. Replacement of the HA/NA subtype of strain (e.g. supplanting the original H5N1 strain with an H7N7 strain). Advice from EU competent authorities should be sought on the regulatory framework and data requirements for such a change.

REFERENCES

1) Note for Guidance on dossier structure and content for pandemic influenza vaccine marketing authorisation (EMEA/CPMP/VEG/4717/03)

2) Cell Culture Inactivated Influenza Vaccines – Annex to Note for Guidance on Harmonisation of Requirements for Influenza Vaccines (CPMP/BWP/2490/00)

3) Guideline on adjuvants in vaccines for human use (CHMP/VEG/134716/2004)

4) Note for Guidance on preclinical pharmacological and toxicological testing of vaccines (CPMP/SWP/465/95)

5) Note for Guidance on Harmonisation of Requirements for Influenza Vaccines (CPMP/BWP/214/96)

6) Note for Guidance on the Clinical Evaluation of Vaccines (CHMP/VEG/164653/05)

European Medicines Agency
Evaluation of Medicines for Human Use

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON DOSSIER STRUCTURE AND CONTENT FOR PANDEMIC INFLUENZA VACCINE MARKETING AUTHORISATION APPLICATION (Revision)

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GUIDELINE ON DOSSIER STRUCTURE AND CONTENT FOR PANDEMIC INFLUENZA VACCINE MARKETING AUTHORISATION APPLICATION

TABLE OF CONTENTS

1. GENERAL INTRODUCTION

1.1. Procedural issues

This guideline provides the basis for a fast track authorisation procedure for pandemic influenza vaccines within the EU. The procedure that is explained in detail below involves the submission and approval of a ***core pandemic dossier*** during the interpandemic period, which is based on a ***mock-up vaccine***. Once a pandemic is declared the procedure allows for fast track approval of a pandemic variation as may be necessary to supplant the vaccine virus in the mock-up vaccine with the final pandemic influenza vaccine virus. For more information on the procedure for the fast-track approval of pandemic influenza vaccines, consult the Guideline on submission of marketing authorisation applications for pandemic influenza vaccines through the centralised procedure (CPMP/VEG/4986/03)

This document should be read in conjunction with the relevant Notes for Guidance, monographs of the European Pharmacopoeia (Ph. Eur.) and other guidance documents as listed in section 6. References.

The Core SPC for pandemic influenza vaccines (CHMP/VEG/193031/2004) should be followed.

1.1.1. Core pandemic dossier

The core pandemic dossier should describe the quality, non-clinical and clinical data relevant to the mock-up pandemic influenza vaccine. Specific guidance on the content of each module of the application is provided in this guideline.

The mock-up vaccine should be produced in the same way as is intended for the final (ie containing antigen from the actual pandemic strain) pandemic influenza vaccine (e.g. inactivated whole virion, split or subunit vaccine derived from virus grown in cell culture or in embryonated hens'eggs). The antigen content, adjuvant system (if used) and route of administration should also be the same as intended for the final pandemic influenza vaccine.

It is expected that the antigens in the mock-up vaccine should be different from those in the influenza viruses that are circulating, in the inter-pandemic period so that the immunogenicity of the vaccine can be assessed in populations with no or low rates of detectable pre-existing immunity. The core pandemic dossier should contain a justification of the antigens chosen for inclusion in the mock-up vaccine

1.1.2. Pandemic variation

The pandemic variation application will contain only the quality data that are new and relevant for the pandemic influenza vaccine virus. It is not expected that non-clinical and clinical data obtained from studies with the final pandemic vaccine would be included in the pandemic variation dossier; Marketing authorisation holders are expected to gather clinical information with the final pandemic vaccine as the influenza pandemic progresses.

1.2. Legal framework

Directive 2001/83/EC, as amended, lays down in Article 8 the requirements for a marketing authorisation application and Regulation (EC) No 726/2004 lays down the procedure for submission to the EMEA via the centralised route.

Commission Regulation (EC) No 1084/2003 of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products granted by a competent authority of a Member State and Commission Regulation (EC) 1085/2003/EC of 3 June 2003 concerning the examination of variations to the terms of a marketing authorisation for medicinal products for human use and veterinary medicinal products falling within the scope of Council Regulation (EEC) No 2309/93. Both Commission Regulations lay

down in Article 8 the requirements for the variation of a marketing authorisation in a pandemic situation with respect to human diseases.

The variation Regulations (EC) 1084/2003 and 1085/2003 will be applicable for any variations to the core pandemic dossier resulting from changes to the original data submitted i.e. manufacturing changes, maintenance activities.

2. SCOPE

This Guideline provides guidance on the documentation to be included in the core pandemic dossier and pandemic variation application for inactivated influenza vaccines.

The development and licensing of a live attenuated pandemic influenza vaccine requires additional considerations not covered by this Guideline. Reference is made to the Point to Consider on the development of live attenuated influenza vaccines (EMEA/CPMP/BWP/2289/01) and specific advice should be sought from European competent authorities.

Other vaccine development strategies will be dealt with on a case by case basis and should be discussed with European competent authorities.

This Guideline does not provide guidance on influenza vaccines produced from viruses with the potential to cause a pandemic, for use from WHO Phase 3 onwards[1].

3 .QUALITY

As for inter-pandemic influenza vaccines, pandemic influenza vaccines shall be produced in either embryonated hens'eggs or on a cell substrate[2]. Influenza vaccines intended to mimic the pandemic vaccines ("mock-up" vaccines) and the pandemic vaccines themselves shall be compliant with the relevant Ph. Eur. monographs for egg-derived and cell derived inactivated influenza vaccines or the CPMP Note for Guidance on Cell Culture Inactivated Influenza Vaccines (CPMP/BWP/2490/00), as appropriate. For the testing for freedom from extraneous agents of the seed virus for the pandemic vaccine (viruses, mycoplasma, bacteria and fungi) alternative approaches may have to be taken in view of time constraints.

3.1. Core pandemic dossier

3.1.1. Candidate influenza vaccine virus

Definition

A candidate influenza vaccine virus ('vaccine virus') is characterised antigenically, genetically and phenotypically and is issued by a WHO Collaborative Centre or by an approved reference laboratory. It is selected to represent an influenza strain that may be considered for mock-up vaccine production. It is the responsibility of the vaccine manufacturer to establish the suitability of the vaccine virus for vaccine production and to establish a vaccine seed lot. Nevertheless, it is recommended that manufacturers consult the competent authority to determine the specific influenza strain subtypes (e.g. H5N1, H9N2 or any other reference virus as indicated below) to be used as a mock-up vaccine virus.

[1] For this type of influenza vaccines, consult the *Guideline on influenza vaccines prepared from viruses with the potential to cause a pandemic and intended to be used outside of the core dossier context* (CHMP/VWP/263499/2006).

[2] If novel cell substrates are used, the applicant will have to provide all necessary characterisation data. See Ph. Eur. General Chapter 5.2.3: Cell substrates for the production of vaccines for human use.

Vaccine virus

The vaccine virus for the core pandemic dossier is likely to be derived from an avian, porcine or human source by one of the following procedures:

a) A reassortant virus containing the haemagglutinin (HA) genome segment of a highly pathogenic virus[3], where the segment has been modified to remove the known determinants of high pathogenicity for avian species, the neuraminidase (NA) segment of the virus and the remaining six segments from an attenuated human influenza virus such as A/PR/8/34 (PR8). The reassortant will be produced by reverse genetics on mammalian cells and may subsequently be grown in eggs or on cells.

b) A reassortant containing the HA and NA genome segments of an apathogenic virus[2] with some or all of the remaining segments derived from PR8. The reassortant will be produced in eggs or on mammalian cells using either conventional technology or by reverse genetics respectively.

c) A non-reassortant 'novel' wild-type influenza virus (pathogenic or apathogenic). Appropriate containment for pathogenic viruses will need to be in place (see Annex 2).

Examples of vaccine viruses suitable for use as mock-up vaccine virus:

- H5N1 reassortant derived from a highly pathogenic strain such as A/Hong Kong/213/2003 or A/Viet Nam/1194/2004 by reverse genetics. In view of the occurrence of human H5 virus infections in recent years, this choice has the advantage of being a potential pandemic strain and being produced by reverse genetics, the most likely method of pandemic vaccine virus development.
- H5N3 avian virus. Vaccines produced from the H5N3 strain A/Duck/Singapore/97 have already been tested clinically. This strain is antigenically close to the highly pathogenic H5N1 strain, A/Hong Kong/156/97.
- H9N2 virus. Human H9N2 viruses such as A/Hong Kong/1073/99 have already been used for experimental vaccine production and have been tested clinically. There is preliminary evidence that individuals born before 1968 may have some residual immunity that enhances H9N2 vaccine immunogenicity. Clinical trials of H9N2 vaccines should therefore be stratified by age.
- H2N2 Human virus. A/Singapore/1/57 is the 1957 pandemic strain and has been recently used for experimental vaccine production. Clinical trials of H2N2 vaccine should take account of residual immunity in persons born before 1968.
- H7N1 reassortant derived from a highly pathogenic avian virus by reverse genetics. H7N1 and H7N7 viruses have been associated with European poultry outbreaks in recent years and H7N7 viruses have been associated with human infections.

Virus quality

The WHO network traditionally develops, in eggs, high yielding influenza vaccine viruses, that are then made available by a WHO Collaborating Laboratory to vaccine manufacturers. Such viruses are either wild-type influenza viruses or reassortants based on PR8. Where the preparation of the vaccine virus involves reverse genetics, there are additional quality considerations beyond those involved with annual vaccine production.

Reverse genetics (options a and possibly b above) requires the use of mammalian cells for development of a vaccine virus and this imposes different requirements to assure the safety and quality of the product. In view of the use of mammalian cells for the development of vaccine virus by reverse genetics, the following minimum set of parameters should be met:

- The cell substrate used to develop the reassortant reference virus has been approved for human vaccine production or should meet the principles of the requirements of Ph. Eur. general chapter 5.2.3. on cell substrates for the production of vaccines for human use.
- Materials used in generating a vaccine virus via reverse genetics process must be compliant with the current version of the Transmissible Spongiform Encephalopathy Note for Guidance.
- Materials used in generating a vaccine virus via reverse genetics process may affect the safety of the vaccine in terms of viral, bacterial, fungal and mycoplasma contamination. Potential safety

[3] In the context of this Guideline, highly pathogenic and apathogenic refer to the presence or absence of a series of basic amino acid residues at the HA cleavage site that are a known determinant of pathogenicity in avian strains.

risks associated with these materials should be taken into account in the applicant's overall safety evaluation for the vaccine (see 3.1.2. ii).
- Detailed laboratory records are maintained. The laboratory records should include documentation that no other influenza viruses or their genetic material are handled at the same time as the rescue work in order to avoid cross contamination.
- The vaccine virus produced has been assessed by a WHO collaborating laboratory to conclude that antigenic, genetic and phenotypic characteristics make the virus suitable for general use. This includes, when appropriate, testing in animals to demonstrate elimination of high pathogenicity[4] (see also in Non-clinical section).
- A protocol is prepared providing a general description of the vaccine virus development.

Safety aspects of the vaccine reference virus

During the development of a mock up vaccine for a core dossier, special consideration must be given to biological containment. Containment issues are outside of the scope of this Guideline. However, some guidance can be found in Annex 1. Manufacturers should adhere to National or Regional Health and Safety regulations.

3.1.2. Vaccine seed lots

Production

i) If an attenuated pandemic influenza vaccine virus obtained through an official WHO influenza collaborating centre is further genetically modified for reasons to be justified, it may be necessary to demonstrate maintenance of attenuation by a suitable test in animals, for example the chicken intravenous pathogenicity test, or a pathogenicity test performed with ferrets, depending on the nature of the new genetic change.

ii) A vaccine seed lot system should be employed. The vaccine seed lots may be prepared in SPF embryonated hens' eggs or on a qualified cell line as used for production.

Qualification

i) The haemagglutinin and neuraminidase antigens of each seed lot are identified as originating from the correct strain of influenza by suitable methods. Usually, specific antisera obtained from a WHO Collaborating Centre for Influenza are used for determination of HA and NA identity. It is possible that reagents may not be available for the chosen mock-up vaccine, so alternative tests to identify the seed virus (e.g. PCR) should be developed for the mock-up vaccine.

ii) Testing for extraneous agents

The vaccine seed virus shall be tested for freedom from extraneous agents (extraneous viruses, bacteria and fungi and mycoplasma) according to the Ph.Eur. monographs for egg-derived inactivated influenza vaccines or the CPMP Note for Guidance on Cell Culture Inactivated Influenza Vaccines (CPMP/BWP/2490/00), as appropriate. Although the use of reverse genetics is expected to reduce the risk of introducing extraneous agents, it is currently difficult to predict the contribution of reverse genetics derived virus seeds on vaccine quality attributes such as extraneous agent contamination. It remains possible that production cells, reagents and substrates which are derived from animal origin could pose a risk with regard to viral safety. Consequently, whilst the extent of the extraneous risk evaluation for vaccine seed virus originating either from classical or reverse genetics techniques for production of influenza vaccine on cell cultures may be different, such a risk assessment should be made in either case.

iii) Where the influenza seed virus is prepared using reverse genetics, the sequence of the HA and NA genome segment of the influenza virus should be verified and compared to the genome segments of vaccine virus to confirm the genetic stability of the production influenza virus. This should preferably be done at the level of the Working Seed Virus, and at the passage level representing the final vaccine for three batches.

[4] The virus will be tested for non-pathogenicity in chickens and ferrets according to protocols approved by the OIE (www.oie.int) and WHO respectively.

3.1.3. Vaccine Production

Production

Growth of vaccine virus shall be either in embryonated hens' eggs or on a qualified cell line. Manufacturers using mammalian cell cultures for vaccine production should refer to the CPMP Note for Guidance on Cell Culture Inactivated Influenza Vaccines (CPMP/BWP/2490/00). Where the production process of the mock pandemic vaccine is based on an established and licensed process, e.g. that for a seasonal influenza vaccine, the process may have to be amended to fulfil the requirements for vaccine production in a pandemic situation. These amendments should be fully explored and validated, as appropriate. The manufacturing development should be detailed in the mock-up MAA.

The European Pharmacopoeia test for abnormal toxicity of the finished product is only required for the validation of the manufacturing process.

Formulation

For multidose preparations intended for the pandemic vaccine, an effective antimicrobial preservative should be evaluated[5], taking into account possible contamination during use and the maximum recommended period after first use (in-use shelf life). Tests for the antimicrobial preservative should be included for the bulk vaccine if appropriate. The applicant should investigate the possible interference of the antimicrobial preservative with other tests.

Vaccine standardisation

It is possible that a pandemic vaccine will contain a different quantity of HA than the 15 µg contained in inter-pandemic vaccines.

Normally, influenza vaccine HA content is measured by the immunochemical single radial immunodiffusion (SRD) assay. It is possible that SRD reagents may not be available for the pandemic vaccine, so alternative tests to standardise the vaccine (e.g. protein content, immunogenicity studies in small animals) should be developed and their use validated for the mock-up vaccine. In any case, special emphasis should be placed on accurate determination of low quantities of HA.

Adjuvants

It is expected that the there will be low rates of detectable pre-existing immunity to the influenza vaccine viruses in the mock-up and final pandemic vaccine. As a result, inclusion of an adjuvant in the formulation may be necessary in order to reduce the amount of antigen needed per dose and/or the number of doses required to elicit presumptively protective immune responses.

For advice on the quality aspects of the adjuvants to be used, consult the CHMP Guideline on Adjuvants in Vaccines for Human Use (EMEA/CHMP/VEG/134716/2004). The core dossier should contain detailed information on the origin of starting materials, production process and control testing of the adjuvant. If applicable, special consideration should be given to the control of the extemporaneous mixing of antigen and adjuvant to ensure a consistent preparation.

Stability

Stability data for the mock-up vaccine should be developed as described in Ph. Eur monograph of Vaccines for Human Use (2008:0153).

A protocol for testing pandemic vaccine stability should be developed, using data from the mock up vaccine.

[5] See Ph. Eur. General chapter 5.1.3. Efficacy of antimicrobial preservation and Monograph 0153 Vaccines for human use.

3.2. Pandemic variation

3.2.1. Vaccine reference virus

Definition

A reference virus for a pandemic vaccine will be characterised antigenically, genetically and phenotypically and be issued by a WHO Collaborative Centre for Influenza or by an approved reference laboratory. It will be selected to represent an influenza strain recommended by WHO for vaccine production. It is the responsibility of the vaccine manufacturer to establish the suitability of the reference virus for vaccine production and to establish a vaccine seed lot.

Reference virus development

The pandemic vaccine reference virus can be derived from avian, porcine or human sources by one of the three procedures specified in section 3.1.1.

In the event that the pandemic virus is highly pathogenic, it will be modified by reverse genetics so that it is no longer pathogenic. Alternatively an apathogenic virus, antigenically equivalent to the pandemic virus may be chosen for vaccine development.

Virus quality

The guidance in section 3.1.1. for the mock-up vaccine derived by reverse genetics is equally applicable to the pandemic vaccine viruses.

A pandemic vaccine reference virus will be provided to vaccine manufacturers by one of the WHO Collaborating Centres and, in accordance with CPMP Note for Guidance on harmonisation of requirements for influenza vaccines. The vaccine virus shall be approved by the CHMP.

Safety aspects of the vaccine reference virus

Special consideration will have to be given to the biological containment when pandemic influenza vaccines are produced (see Annex 2).

National and Regional Health and Safety regulations must also be observed.

3.2.2. Vaccine seed lots

Production

The guidance given for core pandemic dossier also applies to the pandemic variation application. Alternative tests to identify the seed virus (e.g. PCR), developed for the mock-up vaccine, shall be used as long as specific antisera obtained from a WHO Collaborating Centre for Influenza, are not available. When such reagents become available, SRD tests should be used for identity testing.

Testing for extraneous agents

The seed virus for production of the pandemic vaccine shall be shown to fulfil the requirements for freedom from extraneous agents (extraneous viruses, bacteria and fungi and mycoplasma) according to the Ph. Eur. monographs for egg-derived inactivated influenza vaccines or the CPMP Note for Guidance on Cell Culture Inactivated Influenza Vaccines (CPMP/BWP/2490/00), as appropriate. In normal inter-pandemic conditions, the seed virus will not be used for production before the results of such testing are known and compliance has been demonstrated. In a pandemic situation, awaiting the outcome of compendial testing for extraneous agents before starting vaccine production may cause unwanted delays in the availability of vaccine. Therefore a system of parallel testing is recommended: alternative faster tests (e.g. PCR for viruses and mycoplasma, alternative "metabolic" tests or short incubation for bacteria and fungi) can be used to screen the seed virus before use in production and to minimise the chances of rejection of batches due to contaminations; in parallel, the compendial tests can be carried out to demonstrate full compliance of the vaccine.

3.2.3. Vaccine production

Production

The guidance given for core pandemic dossier also applies to the pandemic variation application.

The European Pharmacopoeia test for abnormal toxicity of the finished product is only required on the first three batches.

Appropriate immunogenicity data in animals on at least one batch should support the vaccine virus change between the mock up and the pandemic vaccine. Data on at least 3 batches shall be provided after approval of the pandemic variation to demonstrate consistency of production. (see also Non-clinical section)

Formulation
In the case an antimicrobial preservative is needed (i.e. for multidose preparations), an assay for the antimicrobial preservative should be included for the bulk vaccine testing.

Vaccine standardisation
Depending on the results from the clinical trials with the mock vaccine, a pandemic vaccine may contain a different quantity of HA than the 15 µg contained in the seasonal influenza vaccine.
The alternative tests for vaccine potency, validated for the mock up vaccine, should be used as long as SRD reagents are not available. When SRD reagents become available, they shall be used for potency testing.

Adjuvants
The guidance given for core pandemic dossier also applies to the pandemic variation application.

Shelf life
Vaccine stability testing is to be performed according to the protocol in the core dossier. Out of specification results are to be reported to the authorities.

4. NON-CLINICAL SAFETY AND IMMUNOLOGICAL REQUIREMENTS

4.1. General Considerations

The protective efficacy of pandemic influenza vaccines can only be evaluated during an actual pandemic situation. While immunogenicity of mock-up vaccines can be assessed in humans the immunological parameters that might correlate with efficacy of a pandemic vaccine are unknown. Therefore, data on immunogenicity and protective efficacy obtained in challenge studies in animals may be used to help assess the potential protective efficacy of a mock-up vaccine and, by implication, of the final pandemic vaccine of the same construct.

The safety of a mock-up vaccine can be assessed in humans and safety data from use of the corresponding final pandemic vaccine can be collected during an actual pandemic. However, there are some safety-related issues that may need to be investigated with the mock-up vaccine in non-clinical studies.

4.2. Core pandemic dossier

4.2.1. Primary Pharmacodynamics (Protection and Immunogenicity)

4.2.1.1. Proof-of-Concept of Protection

Challenge studies in a relevant animal model (ferrets are the preferred animals) should provide evidence regarding the potential protective efficacy. These studies should also address the need for and role of the adjuvant, if included. The need for priming with a heterologous virus should be considered and justified.

Challenge should be initially with the homologous vaccine virus. Additional challenge studies using one or more heterologous viruses would provide important information regarding the potential for cross-protection.

Disease markers such as viral shedding, body temperature, body weight loss, behaviour, clinical symptoms as sneezing or nasal rattling, and leukocyte counts are important endpoints. Immunogenicity data should be obtained during challenge studies in order to evaluate whether any correlation exists between antibody response and development or severity of disease[6]. These key data are expected early during development of the product.

4.2.1.2. Non-clinical immunogenicity

Immunogenicity data derived from a small animal species that responds well to human influenza vaccine (e.g. chicken, mice, and ferrets) are expected before starting clinical trials. The investigations should include an evaluation of immune responses according to dose and dose interval using the mock up vaccine virus. If an adjuvant is included immunogenicity studies should address the effect and role of the adjuvant, as indicated in the Guideline on Adjuvants (CHMP/VEG/134716/2004).

Immunogenicity studies in animals are also useful to document consistency of production, in particular during the validation phase of a candidate influenza vaccine manufacturing process. Appropriate immunogenicity data for the first three batches of the mock-up vaccine should be included in the application to document consistency of production. Alternatively, these data could be obtained in clinical studies.

4.2.2. Non-clinical safety (Toxicity testing)

- For split or subunit candidate influenza vaccines that are to be manufactured and formulated similar to the licensed seasonal vaccine (apart from the vaccine virus) or similar to a licensed mock-up vaccine, routine non-clinical toxicity studies need not be repeated, provided that previous studies were performed in accordance with the requirements of the Note for Guidance on preclinical pharmacological and toxicological testing of vaccine (CPMP/SWP/465/95) and were included in the relevant applications.

- Influenza vaccines derived from an entirely new production process or a new formulation will require a complete non-clinical study program as stipulated in the relevant guidelines.

- For new adjuvanting systems applicants should consult the Guideline on adjuvants in vaccines for human use (CHMP/VEG/134716/2004).

In view of the possible use of these vaccines in pregnant women, animal reproductive toxicity studies should be performed and should be available before authorisation. The study design should reflect the clinical dosing schedule (groups with different time points might be considered).

For reduction of, or exemption from, any part of a non-clinical safety investigation program, European competent authorities should be consulted for Scientific Advice.

4.3. Pandemic variation

The only new non-clinical data that need to be submitted are appropriate animal immunogenicity data from at least one batch. Data from at least 3 batches shall be provided after approval of the pandemic variation to demonstrate consistency of production. (see also Quality section).

[6] A theoretical risk for disease enhancement after administration in naïve subjects was raised for Aluminium adjuvanted candidate vaccines based on a strain of influenza virus not previously used in vaccines.

5. CLINICAL REQUIREMENTS

5.1. General considerations for the clinical development programme

This section considers:

- The immunogenicity and safety data obtained with the mock-up vaccine that should be included in the core pandemic dossier. Essentially these data will evaluate the administration of a mock-up vaccine that contains (a) influenza virus(es) to which most of all of the population have no detectable immunity.
- Clinical data to be submitted during an actual pandemic, in accordance with the content of the RMP, that are associated with use of the vaccine containing the actual pandemic vaccine virus.

In addition to the guidance provided below, all the relevant sections of the guidance documents, which can be found in Section 6, need to be considered. WHO guidance documents might also be taken into account.

The extent to which the requirements laid down in Guideline on the Clinical Evaluation of New Vaccines (EMEA/CHMP/VWP/164653/2005) have to be fulfilled depends upon several factors. These include the extent to which the manufacturing processes used to produce any mock-up influenza vaccine are shown to be similar to those used to produce one or more licensed inactivated seasonal influenza vaccine.

5.2. The Core pandemic dossier and the mock up vaccine

Studies should provide a detailed characterisation of the immunological responses to the mock-up vaccine.

In the pre-submission phase applicants are encouraged to present and discuss the clinical development plan and interim results with European competent authorities. At the time of the marketing authorisation application, the applicants should present final immunogenicity and safety data until 6 months post primary vaccination.

5.2.1. Target population

The data provided in the core pandemic dossier may be obtained solely from healthy adults aged from 18 years, with or without data from subjects aged >60 years.

Paediatric data

In a pandemic situation, children may be very vulnerable to infection and so constitute a special target group for vaccination. Therefore, once data have been obtained from adults to support the core pandemic dossier, it is recommended that at least limited data on safety of the mock-up vaccine should be obtained from healthy children[7]. The plan for paediatric studies should be agreed in the Paediatric Investigational Plan (PIP). The results of paediatric trials should be submitted to European competent authorities and, as necessary, may support a variation to the core pandemic dossier.

In the case of an actual pandemic (see section 5.3.4) priority should be given to an assessment of the immunogenicity of the final pandemic vaccine in children. At the time of marketing authorisation the plans for paediatric studies have to be agreed upon in the Risk Management Plan (RMP).

[7] The paediatric data can also be obtained with the corresponding pre-pandemic vaccine, if submitted in parallel.

5.2.2. Design of clinical trials

The clinical development program should be based upon trials that directly compare different dose levels of antigen derived from the candidate influenza vaccine virus(es) for inclusion in the mock-up vaccine.

The primary immunisation schedule, including number of doses and dose intervals, should be justified. If incorporation of an adjuvant is proposed then studies should compare formulations with and without adjuvant and should seek to identify an appropriate antigen-adjuvant ratio.

The numbers of subjects within each clinical trial should be adequate to ensure that the trial is able to fulfil its objectives (see EMEA/CHMP/VWP/164653/2005). Stratification into age categories or into groups with other characteristics that may cause them to respond to the vaccine differently should be employed to ensure that a representative cross-section of the population is studied and sufficient immunogenicity and safety data in each of these strata are presented.

5.2.3. Immunological assessment criteria

The primary objective of the immunogenicity studies is to assess whether the mock-up vaccine would likely elicit adequate immune responses, which might be predictive for protection after replacement of the mock-up vaccine virus with the final pandemic influenza vaccine virus.

Depending on the degree of any existing partial immunity in various age groups of the population to the pandemic virus and the virulence of the strain, influenza infections during a pandemic may be expected to:

- Have a different clinical course compared with infections with inter-pandemic strains, with higher rates of complications and mortality.
- Show a different age distribution than is usual during inter-pandemic periods.
- Show a high rate of infectivity.
- Show a waved pattern of incidence.

Due to all the above issues, it is not anticipated that the immunological criteria that are currently applied to the clinical data supplied for the annual vaccine virus change variation procedures for existing inactivated influenza vaccines are relevant to the assessment of potential pandemic vaccines. Literature review and the results of non-clinical data should be used to obtain information on immunological correlates of protection that might be relevant to a pandemic vaccine. Emphasis should be put on full characterisation of the immune response, including those data obtained in preclinical studies.

However, with no other criteria to suggest at present, it is anticipated that mock-up vaccines should at least be able to elicit sufficient immunological responses to meet all three of the current standards set for existing vaccines in adults and older adults >60 years (CPMP/BWP/214/96) based on haemagglutination inhibition (HI)[8] and/or serum radial haemolysis (SRH)

If these criteria are not met the applicants are urged to further support the immune responsiveness of the vaccine using other assays, such as neutralising antibody assays and if possible, explore cell mediated immunity.

It is expected that serum neutralising antibody (SNA) will also be assessed, at least in a subset of vaccinees. In addition applicants are encouraged to measure anti-neuraminidase antibody and to investigate the cell mediated immunity elicited by the mock-up vaccine, although these responses are still of unknown relevance to protection. However exploratory data in a subset of vaccinees after primary and booster vaccination may provide additional insight into the overall effects of vaccination and the potential usefulness of the vaccine (early) in a pandemic.

For HI, SRH and SNA it is recognised that there is considerable intra- and inter-laboratory variation in methodology and that the actual titres that might be reported from a range of samples can be very

[8] The haemagglutination inhibition determination depends on the assay used (e.g. horse vs turkey erythrocytes).

different. EU regulators are aware that there are efforts ongoing to improve on assay variability and international standards are likely to be developed. It is expected that applicants provide full details of assay validation and controls and that the assays are updated and improved in the light of any new developments and availability of international standards. The applicant is recommended to keep reference serum for future analyses and standardisation.

For all the above assays it is expected that data should be generated against the virus(es) in the mock-up vaccine.

As more data become available during the course of the clinical development programmes with mock-up vaccines the existing immunological acceptance criteria assumed to correlate with protection may need to be redefined. The criteria applied to the total population or to specific target groups may need to be revised and/or entirely new criteria may have to be proposed. The data accumulated may also imply a need to explore different dose ranges and/or different immunisation schedules or may highlight the necessity of using adjuvants. Revisions and proposals for new immunological assessment criteria may be made by applicants and/or by the CHMP. Therefore, companies that are developing mock up vaccines should consult with European competent authorities at regular intervals as may be felt appropriate during the development process.

5.2.4. Vaccination schedule

Considering the naivety of the population and the use of an inactivated vaccine, a single dose primary regimen is unlikely to be suitable for a pandemic situation. A priming schedule with two (or even more) doses of vaccine may be needed, possibly with incorporation of an adjuvant. Thus in addition to the need to determine the optimal dose of the antigens, alternative schedules relevant for the pandemic situation should be explored. The optimal dose, schedule and interval of dose may depend upon:

- Vaccine specific factors, such as type and amount of antigens and content of any adjuvant
- Population specific factors such as age, immunological naivety to the pandemic strain(s)
- The circumstances of use. For example, the regimen needed to urgently achieve seroprotection when there is already local circulation of virus may be different to that which can be used in less urgent situations (such as when the virus is still confined to other areas or in prophylactic vaccination of special populations such as front line health care workers).

Similar vaccination schedule recommendations for all pandemic influenza vaccines to be licensed are highly desirable in a pandemic situation for practical reasons. However, different schedules may have to be studied and licensed.

5.2.5. Safety

The safety database for each mock-up vaccine will inevitably be limited due to the reasons acknowledged above. Nevertheless, the database should be sufficient to detect adverse reactions or events at a frequency of approximately 1%. Follow-up for the evaluation of safety should be at least 6 months and should include at a minimum all the local and systemic reactogenicity parameters defined in CHMP/BWP/214/96. If the mock up vaccine contains a novel adjuvant for which there is no or extremely limited supportive data derived from its inclusion at a similar or higher dose in other types of vaccines, then it is necessary to reconsider this minimal requirement. Advice should be sought from EU regulatory authorities.

If any new issues regarding safety arise during the clinical development programme (whether with the mock up vaccines or from reports regarding other similar vaccines), it may be necessary to specifically address these matters in larger pre-pandemic studies.

It is likely that inactivated pandemic vaccines will contain thiomersal. In accordance with CHMP guidance, the level should be kept to the minimum necessary. The applicant should discuss the final thiomersal content of the vaccine.

5.2.6. Post-approval commitments

There will be limited immunogenicity and safety data for the mock-up vaccine and protective efficacy data will not be obtained. Also, the final pandemic vaccine will have to be approved without immunogenicity data (see 5.3.1 below). Therefore, as part of the post-approval commitments, applicants should have protocols in place at the time of licensure of the mock-up vaccine to ensure that immunogenicity, effectiveness and safety of the final pandemic vaccine are adequately documented during use in the field. Any post-approval commitment after the declaration of the actual pandemic should be conducted in accordance with the CHMP Recommendations for the pharmacovigilance plan as part of the risk management plan to be submitted with the marketing authorisation application for a pandemic influenza vaccine (EMEA/32706/2007)

In addition, immunological investigation should be performed, measuring at least HI and/or SRH and SNA against one or more heterologous strains i.e. drift variants of the mock-up vaccine virus. Due to ongoing drift it is anticipated that these data could be provided on an ongoing basis after initial approval of the core pandemic dossier.

To assess the possible need for revaccination to cover (a) subsequent wave(s) of the pandemic, immune responses should be determined after at least 6 months have elapsed since completion of the primary series in a predefined number of subjects. Follow up data should be collected from at least a relevant subset in which persistence of immunity is evaluated. If applicable (i.e. in case of non-persistent antibodies) responses to booster vaccination should be investigated.

5.3. The Pandemic variation and the Final pandemic Vaccine

5.3.1. Approval of the Pandemic variation

In the case of an actual pandemic, the vaccination programme would need to be implemented as soon as possible[9]. Provided that the mock-up and final pandemic vaccines are similar other than in vaccine virus and the dose schedule is unchanged, the final pandemic vaccine may be approved for use by means of a variation that addresses only the quality issues and without the provision of clinical data. Clinical safety and efficacy should be studied as described below and the results should be reported to the Competent Authorities after approval of the pandemic vaccine.

In case the final pandemic vaccine deviates from the approved mock-up vaccine in aspects other than the vaccine virus, the Marketing Authorisation Holder (MAH) should seek advice from European Competent Authorities.

5.3.2. Post-approval clinical investigations

The MAH should conduct the clinical studies (including a prospective cohort study) as specified in the agreed Pharmacovigilance / Risk Management Plan (see section 5.2.6). This will allow to obtain safety, immunogenicity and efficacy data for the final pandemic vaccines if the situation arises.

The accumulation of immunogenicity, efficacy and safety data should ideally be a co-operative effort between companies and public health authorities[10]. Facilities for the rapid sharing of these data should

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[9] Applicants should also consult the following:

- Guideline on submission of marketing authorisation applications for pandemic influenza vaccines through the centralised procedure (CPMP/VEG/4986/03)
- EMEA Pandemic influenza crisis management plan for the evaluation and maintenance of pandemic influenza vaccines and antivirals (EMEA/198532/2005)

[10] Since several different vaccines are likely to be deployed simultaneously in a pandemic situation without geographical separation of distribution of use, it will likely be possible only to estimate the overall **effectiveness of the vaccination programme**. For the pandemic situation, specific case definitions and case detection definitions should preferably be developed and used consistently. However, these may need to be initiated on an ad hoc basis or may need reconsideration with time as the clinical presentation may change during the late pandemic phase. Protocols should describe the populations to be studied and methods to estimate vaccine

be in place since the information will likely have implications for all the vaccines in use in a single pandemic as well as providing lessons regarding the preparation of intervention strategies for future pandemics. Rapid sharing and rapid review of these data will be important since it may be necessary to implement changes in the vaccine, in the vaccination schedule or programme during the pandemic.

5.3.2.1. Immunogenicity

Each MAH should perform immunogenicity studies with the final vaccine in all age groups, and in subjects with defined high-risk conditions. Priority should be given to evaluating immunological response in children. To expedite the initiation of such studies, suitable protocols should be in place in advance of any pandemic as well as, if possible, an agreement in principle from investigative sites and ethical committees to conduct such studies.

The early post-vaccination immunogenicity data should be submitted to European Competent Authorities as soon as possible and may require a reconsideration of the posology recommendations.

The subjects enrolled into these studies should be followed carefully for the development of influenza. Data from these subjects should be used to develop possible serological criteria for protection.

As it is likely that different products will be used during the vaccination campaign for the pandemic, it is possible that individuals receiving a two dose primary series will be offered vaccines of different manufacturers. In this case immunogenicity data should allow for subgroup analyses of mixed products schedules.

5.3.2.2. Safety

Safety data on the final pandemic vaccine will arise from real life use and from post marketing studies as specified in the Pharmacovigilance / Risk management Plan (see 5.3.2). Special attention should be paid to obtaining safety information from groups that will not be represented largely in studies with the mock up vaccine, such as defined high-risk populations and children.

In addition to the assessment of rates of local and systemic reactions in the immediate post-vaccination period, there are specific longer-term and (very) rare adverse events that need to be evaluated, such as the risk of Guillain-Barré syndrome.

For the final pandemic vaccine, large-scale safety data will be generated using the vaccine during a pandemic. Regular PSURs should be submitted to European competent authorities. The frequency and content of the reporting will be agreed with CPMP.
Reporting on adverse events and the period safety update report during a pandemic should follow as far as possible the CHMP Recommendations for the pharmacovigilance plan as part of the risk management plan to be submitted with the marketing authorisation application for a pandemic influenza vaccine (EMEA/32706/2007)

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effectiveness. Clinical outcomes should at least include age specific morbidity and mortality, including rates of hospitalisation.

6. REFERENCES

- Guideline on submission of marketing authorisation applications for pandemic influenza vaccines through the centralised procedure (CPMP/VEG/4986/03)
- Core SPC for pandemic influenza vaccines (CHMP/VEG/193031/2004).
- Guideline on influenza vaccines prepared from viruses with the potential to cause a pandemic and intended to be used outside of the core dossier context (CHMP/VWP/263499/2006)
- Note for guidance on harmonisation of requirements for influenza vaccines (CPMP/BWP/214/96)
- Cell Culture Inactivated Influenza Vaccines - Annex to note for guidance on harmonisation of requirements for influenza vaccines. (CPMP/BWP/2490/00)
- Points to Consider on the development of live attenuated influenza vaccines (EMEA/CPMP/BWP/2289/01)
- Guideline on Adjuvants in Vaccines for Human Use (EMEA/CHMP/VEG/134716/2004)
- Manual of standards for diagnostic tests and vaccines, 4th edition, OIE (2001). Office International des Epizooties, 12 rue de Prony, 75017 Paris, France (www.oie.int)
- Production of pilot lots of inactivated influenza vaccines from reassortants derived from avian viruses. Interim biosafety risk assessment, WHO Global influenza programme (WHO/CDC/CRS/RMD/2003.5 - November 2003)
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- Influenza vaccine (whole virion, inactivated); Ph. Eur. 01/2008:0159
- Influenza vaccine (surface antigen, inactivated, prepared in cell cultures); Ph. Eur. 01/2008:2149
- Influenza vaccine (whole virion, inactivated, prepared in cell cultures); Ph. Eur. 01/2008:2308
- Vaccines for human use, Ph. Eur. 01/2008:0153
- Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines (CPMP/SWP/465/95)
- CPMP Note for Guidance on the Clinical Evaluation of New Vaccines (CPMP/EWP/463/97).
- CPMP Note for Guidance on the Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95)
- CHMP Recommendations for the pharmacovigilance plan as part of the risk management plan to be submitted with the marketing authorisation application for a pandemic influenza vaccine (EMEA/32706/2007)
- EMEA Pandemic influenza crisis management plan for the evaluation and maintenance of pandemic influenza vaccines and antivirals (EMEA/198532/2005)